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History of the Terminology of Cervical Intraepithelial Abnormalities

The terminology of non-invasive epithelial abnormalities associated with an elevated risk of having or developing invasive cervical carcinoma (preinvasive lesions) has been modified frequently over time as understanding of the underlying biology, and approaches to disease management, have changed. In the late 19th and early 20th centuries, there was a single tier approach, with recognition only of surface or intraepithelial carcinoma [1, 2], subsequently renamed carcinoma in situ (CIS) to reflect the cytological similarity between the constituent cells of these preinvasive lesions, and those of invasive carcinomas [3]. This view, with its attendant binary approach to patient management, prevailed until the 1950s, when the concept that there were preinvasive lesions with cytological abnormality of a lesser degree than CIS was developed [4]. Initially termed 'atypical hyperplasia', amongst other terms, this range of epithelial abnormalities was subsequently named 'dysplasia', which was subdivided into three grades; mild, moderate and severe [5].

In 1967, Richart proposed replacing the term 'dysplasia' with 'cervical intraepithelial neoplasia' (CIN) [6] to reflect the idea that the process of development of preinvasive lesions of the squamous epithelium was a biological continuum, rather than being subdivided into two distinct entities, dysplasia (divided into three grades) and carcinoma in situ. There was relatively widespread adoption of this CIN concept, although some continued to use the term carcinoma in situ in addition to dysplasia, perpetuating the 4-tier system. This practice gradually waned and the 3-tier CIN system has been a mainstay of diagnostic practice, particularly in Europe, since the 1980s [7]. The alternative 2-tier system, which recognises low-grade and high-grade squamous intraepithelial lesions (SILs), has its origins in cytopathology in the late 1980s [8], and has been translated into histopathological use, particularly in North America [9, 10].

HPV Infection and Cervical Intraepithelial Abnormalities

Almost 40 years ago, zur Hausen proposed that the human papillomavirus (HPV) was responsible for the development of cervical carcinoma [11, 12]. The first HPV genome was cloned from a cervical carcinoma in 1983 [13] and, although HPV infection was initially thought to be ubiquitous and unlikely to be the main cause of cervical cancer, improvements in molecular technology led to acceptance that HPV infection is necessary for the development of virtually all (if not all) squamous cell carcinomas, and the majority of adenocarcinomas, of the cervix [14]. The efficacy of HPV vaccination, which prevents both HPV infection and the development of CIN [15], strongly supports this conclusion.

This improved understanding of the relationship between HPV infection and cervical neoplasia, and the mechanisms by which the virus subverts the host cell cycle and induces genomic instability, led to a reassessment of the concept that CIN is a biological continuum. Productive HPV infection, which is associated with coordinated viral gene expression linked to squamous differentiation, leads to koilocytic morphology with variable associated epithelial hyperplasia (most prominent in exophytic condylomata). This may be accompanied by a degree of basal cell disorder, which may be sufficient to

fulfil the criteria for CIN 1. Non-productive (or transforming) infection occurs typically when the coordination between viral gene expression and squamous differentiation is lost, often as a consequence of viral integration into the host genome. Transforming infection leads to cell cycle dysregulation and genomic instability as a result of upregulation of viral early gene (particularly E6 and E7) expression. This is associated with the development of more marked cytological abnormality, fulfilling the criteria for CIN 2 or CIN 3. These considerations challenge the concept that CIN represents a biological and morphological continuum and are more in keeping with a 2-tiered biology. Moreover, transforming infection carries a greater risk of progression to invasive disease [16]. It is important to appreciate that this is not inconsistent with the frequent presence of all grades of CIN in individual specimens from patients as transforming infection typically develops on a background of productive infection.

This concept can be extended to glandular lesions of the cervix. Productive infection cannot occur in glandular epithelium, as it is linked to squamous differentiation. However, transforming infection can occur and it leads to the development of cytological abnormality in the same way as transforming infection of squamous epithelium, with an elevated risk of the development of invasive disease.

The Pros and Cons of CIN and SIL

Broadly speaking, low-grade SIL corresponds to a combination of the categories of CIN 1 and HPV-related changes without CIN; and high-grade SIL corresponds to a combination of CIN 2 and CIN 3. The arguments surrounding the choice of system therefore centre on whether combining these categories is advantageous.

Is CIN 1 different from HPV-related change alone?

The CIN system is based on, first, the identification of a lesion as CIN; and second, grading the lesion. The identification of CIN requires the presence of nuclear abnormalities throughout the full thickness of the epithelium (with or without a degree of nuclear maturation) and the determination of grade

assesses the location and extent of cytoplasmic maturation. For example, a CIN 1 lesion shows full thickness nuclear abnormality, often with nuclear maturation towards the epithelial surface, and cytoplasmic maturation that begins in the lower third of the epithelium. CIN 1 also typically shows HPV-related cytopathic effect, namely koilocytosis. A 'pure' HPV' infection shows all of these features except basal nuclear abnormality and therefore the distinction between these two diagnostic categories is dependent on the identification of this feature, which is subjective. The distinction between a 'benign' (HPV only) and a 'premalignant' (CIN 1) lesion is therefore based on a subjective judgement. Identifying both of these morphological entities as low-grade squamous intraepithelial lesions (SILs), on the basis that they are both forms of productive HPV infection, removes this difficulty. The argument for retaining the distinction rests on the contention that the presence of the features of CIN 1 is associated with a different biological or clinical outcome i.e. a greater risk of either the presence of, or progression to, a higher grade lesion. However, the poor reproducibility of low grade squamous cervical intraepithelial abnormalities [17, 18] makes this difficult, if not impossible, to assess.

Does CIN 2 exist?

The concept of a continuum of abnormality makes the existence of 'CIN 2' inevitable. However, the two-tier model based on HPV biology implies that morphologically identified 'CIN 2' is likely to be a mixed category containing some productive infections that show greater nuclear irregularity (low-grade SIL) and some transforming infections that show greater cytoplasmic maturation (high-grade SIL)[19].

Perhaps more problematic than these terminological considerations is the potential clinical effect of abolition of the CIN 2 grade as conservative management may be appropriate in some circumstances, particularly in women of reproductive age. Recent guidelines on the terminology of squamous lesions of the anogenital tract concede this point and make provision for a hybrid system in which the primary diagnosis is given using the two-tier system but this can be qualified using the CIN system if considered

appropriate [20]. Thus, a lesion that shows greater cytoplasmic maturation could be designated high-grade SIL (CIN 2).

Does p16 immunostaining help?

High-risk HPV infection leads to overexpression of the cyclin-dependent kinase inhibitor p16 in cells that express the viral E7 protein, as a result of interference with the G1/S cell cycle checkpoint involving the retinoblastoma protein. p16 expression with a 'block-type' pattern involving basal keratinocytes (which reflects HPV gene expression) has therefore been widely used as a biomarker of high-risk HPV infection[21, 22]. In the context of this discussion, p16 expression is useful for the discrimination of lesions driven by high-risk HPV infection from those unrelated to high-risk HPV, particularly mimics of high-grade SIL such as atypical immature squamous metaplasia or atrophic changes, but it cannot be used to grade lesions using either the CIN or the SIL terminology. Thus, low-grade SILs produced by high-risk HPV infection are p16 positive, as are high-grade SILs. There may be a role for p16 in the assessment of 'CIN 2' lesions, with 'block-type' p16 positivity favouring a high-grade over a low-grade SIL, but this practice is less well established [20].

Terminology in the UK Cervical Screening Programme

The discussion so far provides a springboard for consideration of the terminology used in the UK cervical screening programme. Historically, the CIN system has been preferred, and indeed this is the recommendation of the current guidelines on histopathology reporting, published in 2012 [23].

Systematic cervical screening, with a 'call and recall' system, was introduced in the UK in 1988 [24]. This coincided with the initial description of the 'Bethesda' terminology, which recommended the use of a 2-tier system for cervical cytology in the USA [8]. However, in 1991, a position paper setting out the views of a working party convened by the British Society for Colposcopy and Cervical Pathology and sponsored by the National Health Service Cervical Screening Programme National Coordinating Network strongly supported the use of the 3-tier CIN system for assessing cervical biopsies in the UK

Screening Programme[25]. Moreover, they recommended introducing an additional term, Basal Abnormality of Uncertain Significance, for those lesions in which there was uncertainty over the diagnosis of CIN. Their main arguments for this position were i) the biology of CIN is a continuum; ii) the CIN system was in widespread use; and iii) it allowed retrospective comparison and comparison with cytology (which also used a 3-tier system). This view was cemented by the publication of the first edition of the formal guidelines for Histopathology Reporting in Cervical Screening[26], in which similar arguments are made for use of the CIN terminology. In addition to the points in favour of CIN, given above, the Bethesda system was considered inappropriate as 'it creates the illusion that intraepithelial neoplasia in the cervix is a two-tier disease, whereas it is well recognised that it forms a continuum' and 'it includes non-neoplastic lesions'. The second edition of these guidelines, published in 2012, reaches a similar conclusion but this is based largely on the ability of the 3-tier system to allow correlation with cytology and to provide continuity with existing databases. Importantly, the limited value of the 3-tier system in guiding clinical management is conceded, with specific recognition that patient management is, for practical purposes, based on a 2-tier system [23].

Given the foregoing discussion of HPV biology, the argument for the use of a 3-tier system based on the biological continuum of CIN is difficult to sustain. Similarly, the contention that a 2-tier system 'includes non-neoplastic lesions' assumes that the morphological features of HPV infection alone can be reliably distinguished from CIN 1 showing the features of HPV infection, which is known to be problematic. Finally, the move to using the 2-tier system for the reporting of cervical cytology in the UK screening programme [27] negates the argument for using a 3-tier histological system for correlation purposes; indeed, it supports the argument for moving to a 2-tier system for both cyto- and histopathology. This leaves the issue of database continuity, which is more difficult to resolve. However, the approximate equivalence of HPV/CIN1 to low-grade SIL, and CIN2/CIN3 to high-grade SIL, makes this less problematic, particularly given the recommendation of the LAST report that the appropriate CIN term can be provided in parentheses after the SIL designation (e.g. high-grade SIL (CIN 2)).

Conclusions

The arguments are now converging on the conclusion that the most appropriate terminology for cervical squamous intraepithelial abnormalities should be 2-tier rather than 3-tier. Given the existence of the Bethesda system, recently endorsed by the Lower Anogenital Squamous Terminology (LAST) project in the USA, and by the WHO classification of female genital tract tumours, the recommended terms are low-grade and high-grade SIL, with the option of including the relevant CIN grade in parentheses. Whilst this at first sight appears to represent only a small change, there is a fundamental conceptual difference between the systems. The CIN system requires, first, the identification of a CIN lesion and then, second, determination of its grade on a continuum, with subsequent division into three grades. The SIL system is based on the existence of two different forms of HPV infection, with productive infection leading to low-grade SIL and transforming infection leading to high-grade SIL.

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